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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,417	03/30/2004	Po-Ying Chan-Hui	25237-12977	5640

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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
06/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/813,417	CHAN-HUI ET AL.	
	Examiner	Art Unit	
	LAURA B. GODDARD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/3/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 9, 2008 has been entered.

Claims 1 and 4 are amended. Claims 2, 3, and 5-45 are canceled. Claims 1 and 4 are currently pending and being examined.

Priority

2. It is noted that the instant application is a CIP of Applications 10/623,057 and 10/154,042, and neither application provides support for the instantly claimed method of diagnosing breast cancer in a patient sample comprising fixed breast tissue sample or a frozen breast tissue sample, comprising measuring directly in the patient sample and amount of Her1-Her-2 complex, Her-2-Her-3 complex or both; comparing each such amount to its corresponding amount in a reference normal breast tissue sample; and correlating differences in the amount or amounts from the patient sample and the respective corresponding amount or amounts from the reference sample, wherein an increase in the amount of Her1-Her-2 complex, Her-2-Her-3 complex, or both, indicates

the presence of breast cancer in the patient. Therefore, it has been determined that the priority date for prior art purposes is the filing date of March 30, 2004.

Specification

3. The specification is objected to for the following reason: The specification on page 1 should be amended to reflect the most current priority status of the present application, including proper reference to applications that have been issued or abandoned. For example, application Ser. No. 10/623,057 **is now US Patent 7,105,308**, and application Ser. No. 10/154,042 is **now US Patent 7,255,999**. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication 2004/0106161, Bossenmaier et al, filed July 14, 2003, published June 3, 2004 in view of Lundy et al (American Journal of Pathology, 1991, 138:1527-1534), Hudelist et al (Breast Cancer Research and Treatment, 2003, 80:353-361), and Yarden (Oncology, 2001, 61 (suppl 2):1-13).

The claims are drawn to a method of diagnosing breast cancer in a patient sample comprising fixed breast tissue sample or a frozen breast tissue sample, comprising measuring directly in the patient sample an amount of Her1-Her-2 complex, Her-2-Her-3 complex or both; comparing each such amount to its corresponding amount in a reference normal breast tissue sample; and correlating differences in the amount or amounts from the patient sample and the respective corresponding amount or amounts from the reference sample, wherein an increase in the amount of Her1-Her-2 complex, Her-2-Her-3 complex, or both, indicates the presence of breast cancer in the patient (claim 1), the method of claim 1 wherein the amount or amounts of said Her-1-Her-2 or Her2-Her-3 complexes are determined by the steps of: contacting complexes in said patient sample with a cleaving probe having a cleavage-inducing moiety with an effective proximity, and with one or more binding compounds each having one or more molecular tags attached thereto by a cleavable linkage, the molecular tags of different binding compounds having different separation characteristics, such that the cleaving probe and the one or more binding compounds specifically bind to their respective complexes and the cleavable linkages of the one or more binding compounds within the effective proximity of the cleavage-inducing moiety thereby releasing one or more of the one or more molecular tags; and separating and identifying the released molecular tags to determine the presence or absence of said complexes in said patient sample (claim 4).

Bossenmaier et al teach a method comprising measuring directly in a patient tumor sample an amount of Her1-Her-2 heterodimer, Her-2-Her-3 heterodimer or both,

wherein the patient sample is from breast cancer and is a biopsy and can be formalin-fixed, paraffin-embedded ([0015-0018]; [0023]; [0095]; [0097]; [[0119-0125]; [0128-0131]; [0140-0159]; Example 3, 4, and 7), wherein heterodimers are measured by contacting the tumor sample with a first binding compound that binds Her-2 and has a detectable moiety that is linked to the first binding compound by a cleavable linker, then contacting the tumor sample with a second binding compound that binds to either Her-3 or Her-1, and not to Her-2, that is capable of cleaving the cleavable linker in the first binding compound if the first and second binding compounds are in close proximity. The presence of heterodimer Her-2-Her-1 or Her-2-Her-3 is detected when the presence of free detectable moiety is identified, which can be identified by capillary electrophoresis, which requires separation ([0019-0022]; [0153-0159]). Bossenmaier et al teach that Her-2 (ErbB2), Her-1 (EGFR), and Her-3 (ErbB3) expression is known in the art to be increased in breast cancer cells ([0005-0014]), that Her-2 is the preferred heterodimerization partner for Her-1 and Her-3, that heterodimerization of Her-2 with Her-1 or Her-3 activates receptor signaling, and that ligand-dependent heterodimerization of Her-2 with Her-1 or Her-3 may promote the growth of tumors that express Her-2 ([0013]). Bossenmaier et al teach that a cancer characterized by excessive activation of an ErbB receptor is one in which the activation of ErbB receptor in cancer cells significantly exceeds the level of activation of that receptor in non-cancerous cells of the same tissue type, and that such excessive activation may result from overexpression of the ErbB receptor in the cancer cells ([0099]). Bossenmaier et al teach that the presence of Her-2-Her-1 and/or Her-2-Her-3 heterodimers indicates that

the tumor will be responsive to treatment with an anti-Her-2 antibody because the antibody will disrupt signaling by the heterodimer ([0015]; abstract).

Bossenmaier et al does not teach a step of directly comparing the amount of Her-1-Her-2 or Her-2-Her-3 heterodimer to the amount measured in a control breast tissue sample.

Lundy et al teach measuring Her-2 (neu) and Her-1 (EGFR) in fixed or frozen breast tumor samples and compare the expression to that found in normal breast tissue, wherein there was no staining observed for Her-2 in normal breast tissue (p. 1529, col. 1; Table 2 and 4). Lundy et al found a high correlation between Her-2 and Her-1 expression in breast cancer (p. 1532, col. 2 through p. 1533, col. 1).

Hudelist et al measure co-expression of Her-1, 2, 3, and 4 in frozen breast tumor samples and detected the co-expression of all four receptors in almost 80% of cases, with the strongest correlation between Her-2 and Her-3 co-expression. This finding is in accordance with previous studies that suggest the significant role of Her-2-Her-3 heterodimers in breast tumorigenesis, wherein coexpression of Her-2 and Her-3 is linked to breast tumor progression (p. 359, col. 1-2). Hudelist et al teach that Her-2 is the preferred co-expression partner and the most likely dimerization candidate in breast tumors (abstract; Table 1; p. 360, col. 1).

Yarden teaches that overexpression of Her-2 is diagnostic of breast cancer (p. 1, col. 2), that Her-2 forms heterodimers with Her-1 and Her-3 and that Her-2 is the preferred dimerization partner (p. 5, col. 1). Yarden teaches that the Her-2-Her-3

heterodimer is he most potent mitogenic combination and is the predominant heterodimer in carcinoma cells (p. 6, col. 1-2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add the step of comparing amounts of Her-1-Her-2 or Her-2-Her-3 heterodimer to the amount measured in a control breast tissue sample in the method of Bossenmaier et al because the combined references (Bossenmaier et al, Lundy et al, Hudelist et al, and Yarden) teach increased expression of Her-2, Her-3, and Her-1 is a characteristic of breast cancer compared to normal tissue, and that increased expression results in increased heterodimerization, and because Bossenmaier et al teach that if the heterodimers are present, the patient already has cancer and their presence determines treatment. One would have been motivated to add the step of comparing normal breast tissue in the method of Bossenmaier et al in order to provide a direct comparison and verify the heterodimers are increased in the breast cancer sample. One of ordinary skill in the art would have a reasonable expectation of success diagnosing breast cancer by adding the step of comparing heterodimer amounts in normal breast tissue to the amounts found in breast cancer because the combined references teach it is known that Her-2, Her-1, and Her-3 overexpression is diagnostic of breast cancer, and that these receptors form heterodimers when overexpressed.

Maintained Rejection

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. **Claims 1 and 4 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting** as being unpatentable over claims 1-7 of copending Application No. **10/813412.** Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of Application No. **10/813412** are drawn to a method of determining disease status of a patient suffering from a disease characterized by abberant expression of one or more Her receptor heterodimers comprising measuring directly in a patient sample an amount of each of one or more Her receptor heterodimers, comparing each such amount to its corresponding amount in a reference sample, and correlating differences in the

amounts from the patient sample and the respective corresponding amounts from the reference sample to the disease status of the patient which are an obvious variant of the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented (see section 9 of the previous Office Action).

6. All other rejections recited in the Office Action mailed April 11, 2007 are hereby withdrawn.

7. **Conclusion:** No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard/
Examiner, Art Unit 1642